1999; 59: 4180-4). Moreover, angiotensin converting enzyme 2 (ACE2) has been recognized as the attachment molecule to the viral spike surface protein, thus termed the "receptor of SARS-CoV-2" (See Y. Qiu, Y.-B. Zhao, Q. Wang, J.-Y. Li, Z.-J. Zhou, C.-H. Liao, X.-Y. Ge, Predicting the angiotensin converting enzyme 2 (ACE2) utilizing capability as the receptor of SARS-CoV-2, Microbes and Infection, https://doi.org/10.1016/j.micinf.2020.03.003).

[0007] Additionally, SARS-CoV-2 spike protein has been revealed to contain a furin cleavage sequence (See Rabaan A A, Al-Ahmed S H, Haque S, et al. SARS-CoV-2, SARS-CoV, and MERS-COV: A comparative overview. Infez Med. 2020; 28(2): 174-184). As such, viral spike protein priming may be mediated through furin protease in addition to TMPRSS2. Furin expression has been demonstrated to be up-regulated by thyroid hormone T_3 and its expression was cooperative with transforming growth factor beta or TGF-β (See Chen R N, Huang Y H, Lin Y C, et al. Thyroid hormone promotes cell invasion through activation of furin expression in human hepatoma cell lines. Endocrinology. 2008; 149(8): 3817-3831. doi:10.1210/en.2007-0989). Thyroid hormone T_3 or T_4 binds to thyroid hormone receptor (TR), which then activates genes containing thyroid hormone response elements (TREs) in the regulatory regions of target genes. As such, a furin protease inhibitor, a modulator of T_3, a modulator of T_4, a TR inhibitor, or a TGF-β inhibitor (TGF-βi) are envisioned to be used in combination with an anti-androgen to limit the expression of TMPRSS2 and furin.

[0008] Males infected with SARS-CoV-2 are more likely to be admitted to the ICU compared to females. Various theories have been put forward to explain this disparity. Previously, we have reported that among hospitalized COVID-19 patients, 79% presented with male pattern baldness compared to 31-53% that would be expected in a similar aged match population. Male pattern baldness is known to be mediated by variations in the Androgen Receptor (AR) gene. In addition, the only known promoter of the enzyme implicated in SARS-CoV-2 infectivity is an androgen response element. The polyglutamine repeat (CAG repeat) located in the first exon of the AR gene is associated with androgen sensitivity, testicular cancer and androgenetic alopecia. These observations led us to hypothesize that variations in the AR gene may pre-dispose male COVID-19 patients to increased disease severity; therefore, we conducted a prospective longitudinal study of hospitalized COVID-19 male patients. ICU admission rates for patients with a short (<22) CAG repeat were compared to ICU admission rates for patients with a long (>=22) CAG repeats. Consistent with our hypothesis, 45% of patients with a short CAG repeat were admitted to the ICU compared to 70% of patients with a long CAG repeat (p=0.0429). Compared to hospitalized COVID-19 male patients with a short CAG repeat, hospitalized COVID-19 male patients with a long CAG repeat had a significantly increased risk for admissions to ICU (RR 1.5630, 95% CI: 1.0022 to 2.4378, p=0.0489). Further, the average duration of hospitalization for patients with a long CAG repeat was 37 (+/−21) days compared to 27 (+/−20) days for patients with a short CAG repeat. We believe this is the first study to demonstrate a direct association between androgen receptor genetic variants and COVID-19 disease severity. If the results of our study are replicated in a larger cohort, genetic testing could potentially help identify patients at increased risk for COVID-19 disease severity.

[0009] Additionally, TR regulates gene expression by binding to TREs in DNA either as monomers, heterodimers with other nuclear receptors. One important nuclear receptor that TR forms dimers with is the retinoid X receptor (RXR), a nuclear retinoic acid receptor. TR/RXR heterodimers are the most transcriptionally active form of TR. As such inhibition of RXR would inhibit TR activity.

[0010] The present invention relates to systems, methods, compositions and for diagnosing and treating a viral respiratory infection which may include first measuring polymorphisms in the androgen receptor gene or polymorphisms in genes under regulatory control of the androgen receptor. Identification of polymorphisms in the androgen receptor gene can be used to guide treatments of viral respiratory diseases or infections. Treatments for viral respiratory diseases may include, but are not limited to, androgen receptor antagonists, androgen synthesis inhibitors, or antigonadotropins used in combination with TGF-β inhibitors, thyroid hormone receptor inhibitors, thyroid inhibitors, or furin protease inhibitors. Specifically, the present systems, methods, compositions and kits are useful for treating, preventing, and diagnosing viral respiratory disease as a result of coronavirus infection, e.g., SARS-CoV-2 (COVID-19).

DETAILED DESCRIPTION

[0011] As used herein, the terms "prevent" or "prevention" and other derivatives of the words, when used in reference to viral respiratory infection, e.g., viral respiratory infection, refer to a reduced likelihood of viral respiratory infection in an individual receiving a given treatment relative to that of a similar individual at risk for viral respiratory infection but not receiving that treatment. As such, the terms "prevent" and "prevention" encompass a treatment that results in a lesser degree of viral respiratory infection, e.g., viral respiratory infection, than would be otherwise expected for a given individual. Efficacy for prevention of viral respiratory infection, e.g., viral respiratory infection, can be established through controlled studies, e.g., in which a subject is administered a treatment (e.g., an inhaled treatment) and another subject is administered a placebo. Under these circumstances, if the subject treated with the inhaled treatment undergoes less severe viral respiratory infection symptoms over time relative to the subject receiving the placebo, e.g., at least 5% less, at least 10% less, at least 15% less, at least 20% less, at least 25% less, at least 30% less, at least 35% less, at least 40% less, at least 45% less, at least 50% less or beyond, the treatment is effective for the prevention of viral respiratory infection.

[0012] As used herein, the terms "treat," "treatment," or "treating" refer to therapeutic treatments, wherein the object is to reverse, alleviate, ameliorate, inhibit, slow down or stop the progression or severity of a disease or condition, e.g., SARS-CoV-2 infection or another form of viral respiratory infection. The term "treating" includes reducing or alleviating at least one adverse effect or symptom of a disease or condition, e.g., SARS-CoV-2 infection or another form of a viral respiratory infection. Treatment is generally "effective" if one or more symptoms are reduced. Alternatively, treatment is "effective" if the progression of a disease is reduced or halted. That is, "treatment" includes not just the improvement of symptoms, but also a cessation of, or at least